# Mathematical Foundations of Neuroscience - Lecture 1. Basic facts about the brain and its analysis.

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# About the lecture

- The lecture is aimed at graduate (IV and V year) and PhD students of Mathematics and/or Computer Science
- There will be some mathematics!
- There will be some programming!
- There will be many opportunities to learn fascinating stuff and run interesting simulations!
- Materials and presentations will be available at my web page `http://www.mat.umk.pl/~philip`

# Prerequisites

- everybody needs their brains
- properties of matrices,
- eigenvalues, eigenvector decomposition
- numerical solutions, problems of numerical stability,
- differential equations,
- schemes for solving differential equations
- elementary Matlab and/or C/C++ programming skills.

Most of the prerequisites are welcomed but not entirely necessary (except for the brain and an open mind), as I will briefly recall any mathematical facts before we need them.

# Lecture contents

- Basic information about the brain - its large scale structure, consequences of various damages, methods of brain analysis and imaging. Brain/mind question.
- Neurons and their electrophysiological properties. Hodgkin-Huxley findings and formulation of their equations, action potentials and synapses.
- One dimensional dynamical systems, hysteresis, bistability, phase space analysis, bifurcations and their analysis, integrate and fire models.
- Two dimensional systems, vector fields, equilibria and local linear analysis. Phase portraits and bifurcations.

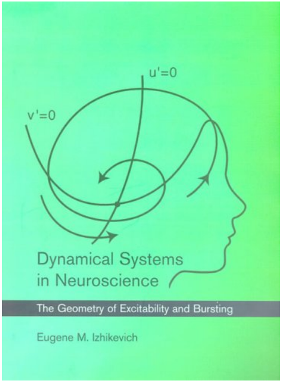
# Lecture contents - continued

- Conductance based models and their properties. Reductions to simple models, FitzHugh-Nagumo model, E. Izhikevich simple model.
- Bifurcations of two dimensional dynamical systems and their significance in neuronal excitability.
- Simple neuronal models of various parts of the brain. Bursting, electrophysiology and mathematical interpretation in simplified models.
- Synchronization, modeling synapses, weak coupling, phase resetting curves. Hebbian learning, Spike Timing Dependent Plasticity and spike prop algorithm.
- Numerical simulations of large scale neuronal ensembles, goals and obstacles.

# Exam

- The lecture will end with an exam. An exam is a perfect opportunity to learn things we thought we knew...
- The exact form of the exam is not yet decided,
- Most probably the exam will be oral
- The exam will be available in both Polish and English, though It might be easier to pass English version due to insufficient vocabulary in Polish language
- Students performing exceptional projects in the Lab can expect various benefits, including exempt from the exam!!!

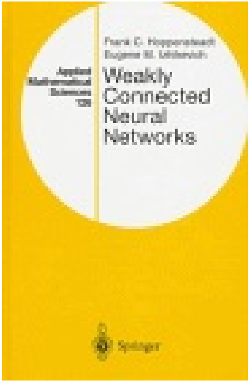
# Dynamical Systems in Neuroscience




Eugene M. Izhikevich, MIT Press 2007

Basic book supporting the lecture.
http://izhikevich.org/publications/dsn/index.htm

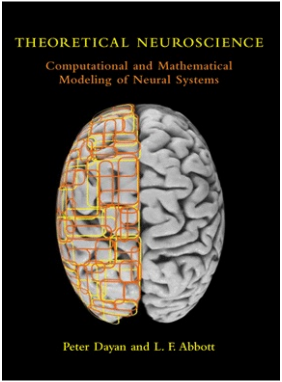
# Weakly connected neural networks




Frank C. Hoppensteadt, Eugene M. Izhikevich, Springer 1997

More advanced book dealing with more advanced subjects.

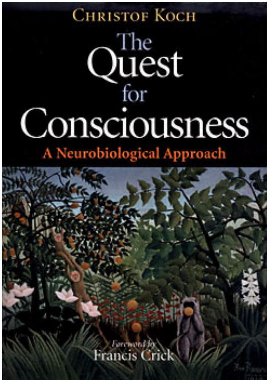
# Theoretical Neuroscience




Peter Dayan, L. F. Abbott, MIT Press 2001

Quite useful book, with some mathematics.

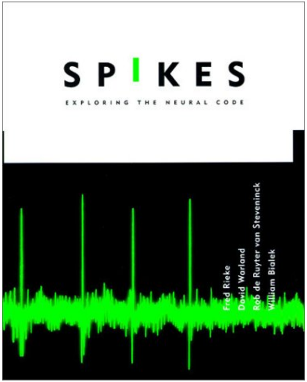
# The quest for consciousness




Christof Koch, Roberts & Company Publishers 2004

Well written book on neuroscience, no mathematics.

# Spikes: Exploring the Neural Code




Fred Rieke, David Warland, Rob de Ruyter van Steveninck, William Bialek, MIT Press 1999

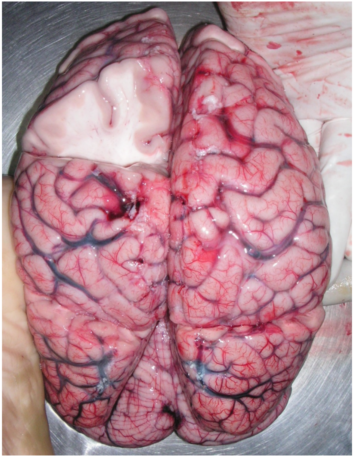
Nice book on neural signaling.

# Scholarpedia

Scholarpedia - the peer-reviewed open-access encyclopedia written by scholars from all around the world.

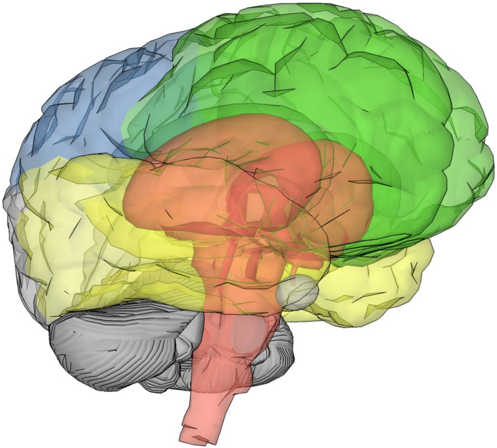
www.scholarpedia.org

# The brain



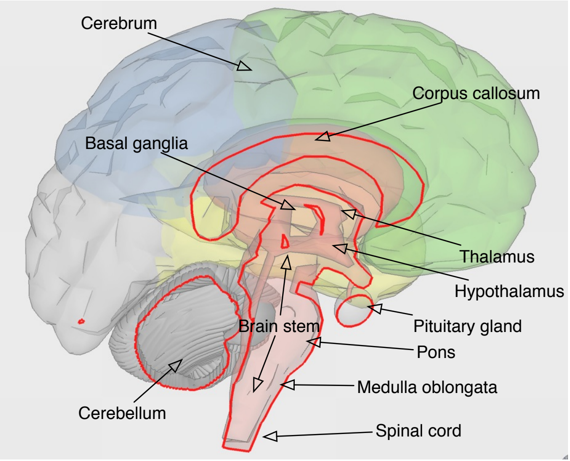
Human brain weights around 1.5 kg, takes volume of about 1.2 liters. Tan-gray on the outside, yellow-white on the inside. Contains between 50-100 billion ($10^{11}$) neurons each having on average 10000 synapses, which in total gives astronomical number of $10^{15}$ synapses... The brain is a marvelous massively parallel biological computer, the hardware that runs our software minds.

# Brain anatomy



The brain is far from being uniform. One can easily distinguish various structures.

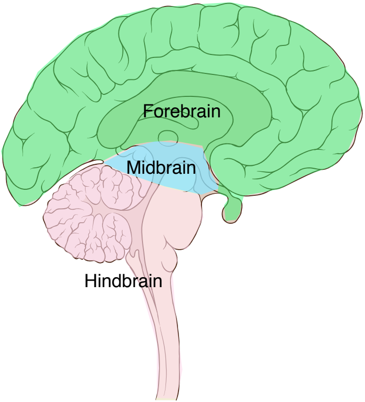
# Brain anatomy




The most obvious is the distinction of the spinal cord followed by the brain stem and Cerebellum. On top of those we find thalamus and basal ganglia. As we move upper we enter cerebrum divided into two hemispheres connected via corpus callosum, a bunch of millions of neural fibers.

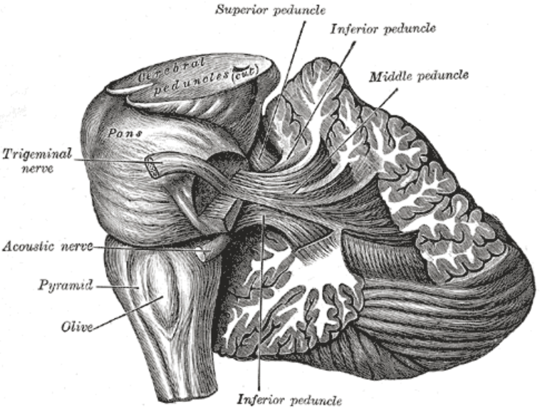
# Divisions of the brain

For various functional, anatomical and developmental reasons the brain is divided into three main parts:



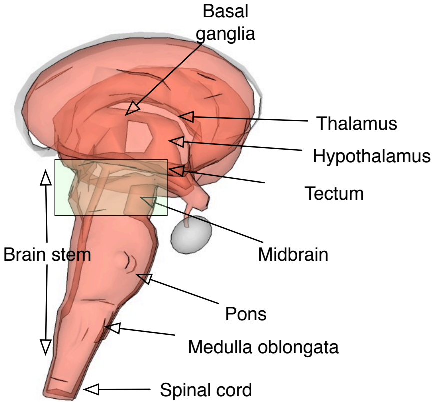

- Hindbrain (Rhombencephalon) further subdivided into Myelencephalon and Metencephalon
- Midbrain (Mesencephalon)
- Forebrain (Prosencephalon) subdivided into Diencephalon and Telencephalon

# Hindbrain



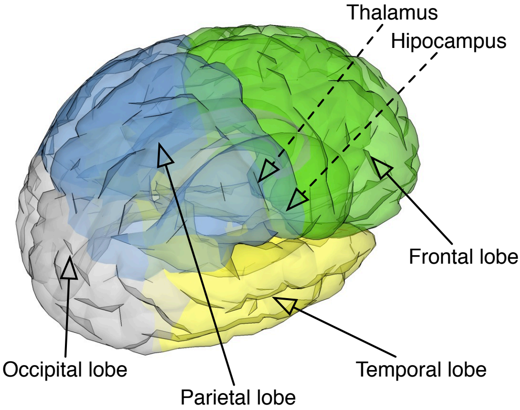

Hindbrain is further subdivided into Myelencephalon containing medulla oblongata (which directly extends to the spinal cord) and Metencephalon composed of the pons and the cerebellum.

# Midbrain




Midbrain is placed on top of Pons, underneath thalamus. This part is composed of tectum ("top of the brain") and cerebral peduncle. In non-mammalian vertebrates parts of tectum (in particular superior colliculus) play role similar to that of primary visual cortex in mammals.

# Forebrain




Forebrain is the largest and the most complex part of a mammalian brain. It is exceptionally large in humans, therefore it is believed to host higher cognitive functions and consciousness. The division into lobes is not based on anatomical reasons. It reflects the names of skull bones covering the cortex.

# Forebrain

Forebrain (composed of diencephalon and telencephalon) has important anatomical features:

- There are two hemispheres, the structures are mirror symmetric
- Internals of the forebrain (white matter) are composed of neuronal fibers
- The external surface of the forebrain is called cerebral cortex. It is where most of information processing is done.
- The cortex is folded to fist large surface inside small cranium. There are ridges and fissures called gyrus (pl. gyri) and sulcus (pl. sulci) respectively.

# Forebrain

- Thalamus and basal ganglia mediate in most of connections to and from the cortex to midbrain and nerves. Information from senses is also routed through thalamus except of olfaction which is connected to the cortex via the olfactory bulb.
- Cortex is mostly recurrently connected to itself. Both hemispheres are connected via massive set of more than 200 million neuronal fibers called the corpus callosum.
- Though strongly symmetric, hemispheres differ substantially. Most people have one dominating hemisphere (usually left one) which is responsible for verbal thinking and speech.

# Forebrain

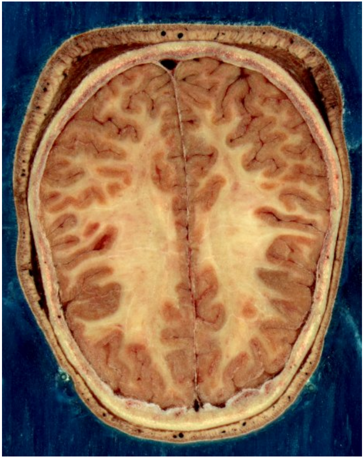
- It seems that the two hemispheres are in fact two brains! Patients who had their corpus callosum cut (Corpus callosotomy) in order to stop epileptic seizures, experience strange "internal conflicts" (one hemisphere decides on something, but the other wants something else).
- Various parts of the cortex, perform different cognitive tasks, related to visual and auditory perception, motion, integration of sensory stimuli, consciousness, speech, decision making, imagination, prediction etc.

# Brain study

Since the brain is such a magnificent organ, which hosts our mind it is wort every effort to study its function. Methodologies include:

- Post mortem studies - most of our knowledge of brain anatomy is obtained that way
- Study of patients with brain damages caused by strokes or accidents
- Brain imaging - from X-ray to magnetic resonance, these methods enable us to observe brain activity correlates on a living subject
- Reading out electric activity via EEG or more directly vie electrodes placed directly inside the brain
- Direct stimulation via electrodes or indirect via strong magnetic pulses
- Injecting anesthetics and neuroactive substances (taking drugs!)

# Post mortem studies



Autopsies are a main source of knowledge about human anatomy. The brain is no exception, and has been studied extensively for many years. This is the only source of information about micro anatomy, types of neurons, structure of the cortex. Special staining techniques also allow for tracking wires (myelinated axonal fibers).

# Brain damages

Crude as it may seem, brain damages are an essential source of knowledge about functional properties of the brain. Of course nobody is damaging brain purposefully (unless it is necessary for medical reasons, like stopping epileptic seizures). Quick facts:

- A human can live (in a deep irreversible coma) with his cerebral cortex totally removed.
- Cutting corpus callosum (Corpus callosotomy) results in surprisingly faint cognitive deficits
- Damages to primary visual cortex (V1) introduce blindness, though the patient can still unconsciously "see" via other visual pathways (the condition is called blindsight)

# The story of dr Jill Bolte Taylor

Dr Jill Bolte Taylor is a trained and published neuroanatomist. She experienced a severe stroke in the left hemisphere of her brain in 1996. It is worth to have a look at her book *My Stroke of Insight: A Brain Scientist's Personal Journey* (published in 2008 by Viking Penguin), as well as her talk at TED conference: http://www.ted.com/talks/lang/eng/jill_bolte_taylor_s_powerful_stroke_of_insight.html

# Electroencephalography (EEG)

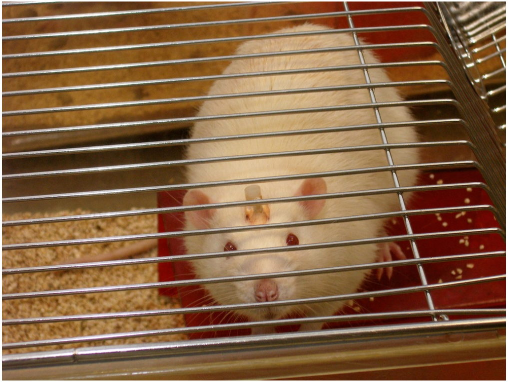
- The brain is an electric device, and consequently it is a source of electromagnetic field
- The field can be recorded by a set of electrodes sticked to the head in certain places
- The recorded signal is greatly averaged, there is now way to track a single neuron with EEG!
- Nevertheless it turns out, that the averaged brain activity has periodic components. Depending on the frequency of the dominating waveform the brains mode of operation can be inferred.
- EEG is therefore very useful in monitoring unconscious patients, tracking sleep phases etc. Flat EEG is a signal of brain death.

# Brain rythms

| | | |
|---|---|---|
| Delta | $< 4$ Hz | slow wave (NREM) sleep |
| Theta | 4–7 Hz | drowsiness, idling |
| Alpha | 8–12 Hz | relax, closed eyes, daydreaming |
| Beta | 12–30 Hz | anxious thinking, active concentration |
| Gamma | 30–100 Hz | The most mysterious brainwaves, "Gamma rhythms are thought to represent binding of different populations of neurons together into a network for the purpose of carrying out a certain cognitive or motor function." |

Table: Brain rythms

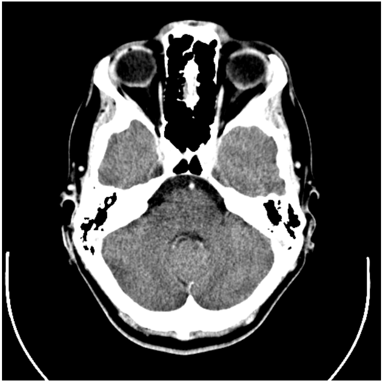
# Cellular recordings



A set of tiny electrodes are implanted into a rodents brain. Slowly the wires are inserted into deeper layers (avoiding any significant damages) until they reach say hippocampus or brain stem.

Figure: A rat with a bunch of its neurons monitored in real time.

# Tomography



Tomography is one of the most useful medical imaging techniques. It allows to gather a number of slices through the body. But how does it work?

# Radon transform

The essential fact underlying tomography is that a certain image transform (Radon Transform) is reversible.

- The object is being x-rayed from every angle in $(-\frac{\pi}{2}, \frac{\pi}{2})$
- As an output we get the so called sinogram
- Such a sinogram has to be cleverly untwined to get the actual slice

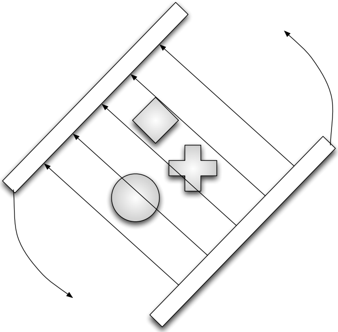


Figure: Sketch of the tomographic procedure.

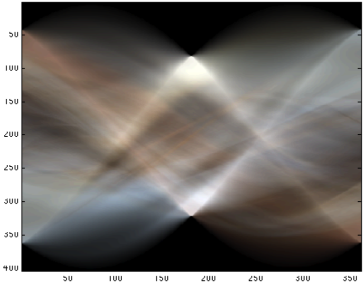



Figure: A sample image and its sinogram.

# Untwining the Radon Transform - Projection-slice theorem

## Theorem (Projection-slice)

*Fourier transform of a projection of 2d image on a 1d line is equal to the 1d slice of the Fourier transform of the complete image (under the same angle).*

Therefore having a sufficiently dense sinogram one can reconstruct the Fourier transform of the original image! Then using inverse Fourier transform one can get back the image itself.

# Projection-slice theorem - sketch proof

PROOF. Without loosing generality we may assume to project on the x axis. Then:

$$p(x) = \int_{-\infty}^{\infty} f(x,y)dy \tag{1}$$

The Fourier transform of $f(x,y)$ is:

$$F(\omega_x,\omega_y) = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} f(x,y)e^{-2i\pi(x\omega_x+y\omega_y)}dxdy \tag{2}$$

# Projection-slice theorem - sketch proof

PROOF. Consequently the slice of the transform:

$$
\begin{aligned}
s(\omega_x) = & F(\omega_x, 0) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} f(x, y) e^{-2i\pi x \omega_x} dxdy = \\
& = \int_{-\infty}^{\infty} \left[ \int_{-\infty}^{\infty} f(x, y) dy \right] e^{-2i\pi x \omega_x} dx = \\
& = \int_{-\infty}^{\infty} p(x) e^{-2i\pi x \omega_x} dx = \widehat{p}(\omega_x)
\end{aligned} \tag{3}
$$

QED. ∎

# Untwining the Radon Transform - Filtered Backprojection

- The projection slice theorem gives quick and elegant proof that the Radon transform is in fact reversible. Unfortunately applying this technique to real images gives very poor results due to numerical instabilities.
- There is another clever technique to untwine the transform, called the Filtered Backprojection. This algorithm is numerically stable and efficient, but its mathematical foundations are much more delicate (though very elegant).
- Following few slides give a short explanation, I encourage to read through and understand the principles, though for younger students this might require considerable effort.

## Untwining the Radon Transform - Filtered Backprojection

Recall that the Radon transform is defined:

$$g(s,\theta) = R(f) = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} f(x,y)\delta(x\cos\theta + y\sin\theta - s)dxdy \quad (4)$$

We shall define the backprojection operator as follows

$$B(g(s,\theta))[x,y] = \int_{0}^{\pi} g(x\cos\theta + y\sin\theta, \theta)d\theta \quad (5)$$

The operator spreads all of the projections back on the plain. The resulting image would obviously be very blurry.

# Untwining the Radon Transform - Filtered Backprojection

Consider the following composition:

$$\begin{aligned} B(g)[x,y] &= B(R(f))[x,y] = \\ &= \int_0^{\pi}\int_{-\infty}^{\infty}\int_{-\infty}^{\infty} f(u,v)\delta(u\cos\theta + v\sin\theta - x\cos\theta - y\sin\theta)dudvd\theta = \\ &= \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} f(u,v)\left(\int_0^{\pi}\delta((u-x)\cos\theta + (v-y)\sin\theta)d\theta\right)dudv = \end{aligned} \tag{6}$$

Now lets examine the integral in parenthesis (variables have been substituted for clarity):

$$d(r,w) = \int_0^{\pi}\delta(r\cos\theta + w\sin\theta)d\theta \tag{7}$$

This integral operator acts like a radial broom, sweeping the whole plain in search for non zero values ($\delta$ is Dirac delta). But for any fixed $r$ and $w$ this integral seems to be zero! Shouldn't it follow that the whole composition is zero?

The problem is, that operator $d$ is not a typical function but rather a distribution

$$d(r,w) = \int_0^{\pi} \delta(r\cos\theta + w\sin\theta)d\theta \tag{8}$$

Observe how $d$ acts inside an integral, multiplied by a characteristic function $I_A$ of some planar subset:

$$\int I_A(r,w) * d(r,w)drdw = \int_A \int_0^{\pi} \delta(r\cos\theta + w\sin\theta)d\theta drdw \tag{9}$$

This integral will compute the measure of set $A$ multiplied by a fraction of "time" (angle) the "broom" spends in $A$ while sweeping the plain! By sampling with infinitesimally small sets of measure $\varepsilon$ the outcome will always be inversely proportional to the distance of sampled set from the origin. For $A$ whose distance from $[0,0]$ is $l = \sqrt{l_r^2 + l_w^2}$ the outcome will be

$$\int I_A(r,w) * d(r,w)drdw \approx \frac{\varepsilon}{l} = \frac{\varepsilon}{\sqrt{l_r^2 + l_w^2}} \tag{10}$$

Getting back to the original composition:

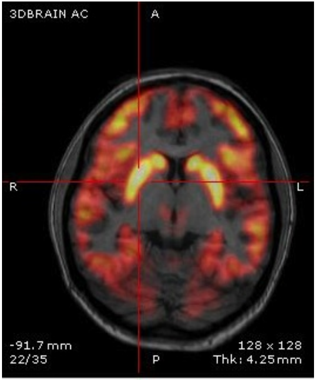
$$\begin{aligned} B(g)[x,y] &= B(R(f))[x,y] = \\ &= \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} f(u,v)\left(\int_0^{\pi}\delta((u-x)\cos\theta+(v-y)\sin\theta)d\theta\right)dudv = \end{aligned} \tag{11}$$

since the distribution in parenthesis is inside the integral, it can be substituted with its density (as estimated on previous slide):

$$\begin{aligned} &= \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} f(u,v)\left(\int_0^{\pi}\delta((u-x)\cos\theta+(v-y)\sin\theta)d\theta\right)dudv = \\ &= \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} f(u,v)\frac{1}{\sqrt{(u-x)^2+(v-y)^2}}dudv = \\ &= f(x,y) ** \frac{1}{\sqrt{x^2+y^2}} \end{aligned} \tag{12}$$

We get the original function (image) convoluted with a known kernel. We can now construct a sharpening filter by finding inverse of $\sqrt{x^2+y^2}^{-1}$ in the frequency domain.

# Positron emission tomography (PET)




In this technique, a short-lived radioactive tracer isotope, is injected into the living subject. As the radioisotope undergoes beta decay it emits a positron, an antiparticle of the electron. Shortly the positron hits an electron (there are plenty electrons in the body), and they annihilate producing a pair of gamma photons moving in (nearly exactly) opposite directions. These pairs of photons are detected and visualized.

# Positron emission tomography (PET)

- The spatial resolution o PET is limited. Firstly a positron can fly an order of millimeters before it hits an electron. Secondly only small portion of gamma photons is detected. The occurrences are averaged and the image can be reconstructed via backprojection similarly to x-ray tomography.
- The PET scan is usually done together with x-ray tomography in the same device, to map positron emission sites on anatomic background.
- The use of short-lived radionuclides (such as carbon-11 ( 20 min), nitrogen-13 ( 10 min), oxygen-15 ( 2 min), and fluorine-18 ( 110 min)) requires a nearby cyclotron.
- The exposure of a patient to the radiation is strictly limited!

# Magnetic resonance

- X-ray tomography is very helpful, but lacks contrast for soft tissues (x rays are mostly absorbed by bones).
- To overcome these limitations another, much more complex and technologically demanding technique has been devised
- The so called magnetic resonance produces images much like a tomogram, but with tremendous soft tissue contrast
- The device requires **superconducting helium cooled magnets** and much more sophisticated imaging algorithms...

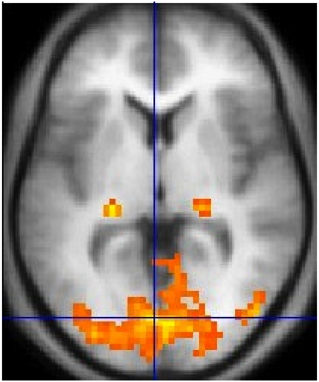
# Magnetic resonance

MRI delivers much more detailed images of soft tissues (in particular the brain) compared to x-ray tomography. But how does it work?

# Magnetic resonance - working principles

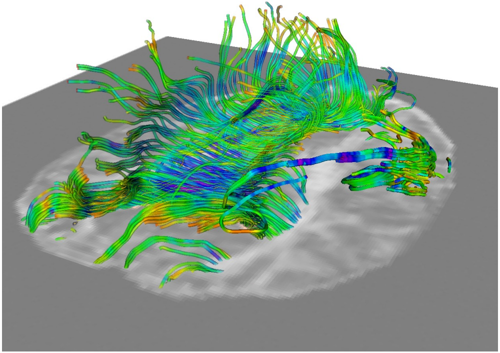
- The patient is placed in a strong magnetic field (1.5-3 Tesla)
- The field causes the water molecules to align with the direction of the field
- A radio frequency electromagnetic field is then briefly turned on, causing the molecules to alter their alignment relative to the field.
- When this field is turned off the molecules return to the original magnetization alignment, emitting electromagnetic signal which is picked up by receiver.
- The response (resonant) frequency depends on the strength of the magnetic field, which is varied by gradient coils. That way the position of respective molecules can be inferred.

# Functional Magnetic Resonance Imaging (fMRI)



The MRI scanner can receive and process many other signals. One such signal is related to hemoglobin which is diamagnetic when oxygenated but paramagnetic when deoxygenated. By tracking the changes in blood oxidization, the scanner can pick up sites consuming much oxygen. In general oxygen consumption in neural tissue correlates with neural activity...

# Difusion tensor imaging (DTI)



MRI is also capable of measuring local diffusion properties of water. Fortunately the diffusion of water in neuronal fibers is anisotropic (it is much faster along the direction of the tracts). MRI can extract the whole diffusion displacement tensor, but in particular the direction of largest component correspond to the direction of the nerve fibre.

# Difusion tensor imaging (DTI)

- The effect of a DTI scan is a vector field with millimeter resolution
- The field can the be used to track individual fibers of thalamo-cortical and cortico-cortical connections!
- Of course a single nerve fibre is a lot smaller and could not be tracked individually in a living brain, but at least DTI gives some average connectivity information. Furthermore the data is global!
- This method is very promising for diagnosing medical disorders and creating large scale computer models of human brain!

# Dictionary (some of the terminology in Polish)

Medulla oblongata - rdzeń przedłużony
Pons - most
Thalamus - wzgórze
Spinal cord - rdzeń kręgowy
Cerebellum - móżdżek
Basal ganglia - jądra podstawne
Corpus callosum - ciało modzelowate, spoidło wielkie
Mesencephalon - śródmózgowie
Diencephalon - międzymózgowie
Telencephalon - kresomózgowie
Metencephalon - tyłomózgowie

Brain stem - pień mózgu
Pituitary gland - przysadka mózgowa
Hypothalamus - podwzgórze
Cranium - czaszka
Occipital lobe - płat potyliczny
Temporal lobe - płat skroniowy
Parietal lobe - płat ciemieniowy
Frontal lobe - płat czołowy
Olfactory bulb - opuszka węchowa
vertebrate - kręgowiec

- Brain is an enormously complex organ whose wiring looks much like those found modern data centers. A human at the age of 20 has between 150000-180000 km (!) of neuronal fibers in his brain...
- Nevertheless the brain is being extensively studied on molecular, cellular and anatomic scale. Clever methods of brain imaging have been developed. These tools are used on a daily basis in hospitals all over the world to help diagnose patients with tumors, hemorrhages and other brain damages.
- Everything in the world is telling that the brain is the host for our minds, our consciousness. Damages to the brain cause inevitable damages to our perception, self-awareness, cognitive abilities, our mind...